

been amended to recite proper dependency. Claim 21 is a rewritten version of claim 20 in order to better claim the subject matter which the inventor regards as the invention and for improved clarity. Therefore, no new matter has been added in this Amendment.

Claim Rejections under 35 U.S.C §102:

Claims 2, 4, and 20 stand rejected under 35 U.S.C §102(b) as allegedly anticipated by Rubenstein *et al.* as evidenced by Shih *et al.*, Liu *et al.*, and the annotation in the Swiss Protein Database. Applicant respectfully traverses this rejection.

Claims 4 and 20 have been canceled without prejudice. New claim 21 has been entered to better claim the subject matter which the inventor regards as the invention. Claim 21 defines a method of predicting a risk for metastasis of a prostate cancer cell by measuring the level of one antigen (*i.e.*, MUC18) immunologically using the antibodies specific for an epitope present in the MUC18 polypeptide whose amino acid sequence is given in SEQ ID NO: 2. If the MUC 18 polypeptide is detected in a given prostate cancer cell by the claimed method, it is predicted that the prostate cancer cell is likely to metastasize. None of the cited references teaches the claimed invention. Rubenstein *et al.* uses a battery of immunohistochemical assays using six antisera to develop an index for characterizing prostate carcinoma. One of the antibodies, Leu-7 monoclonal antibody, reacts with HNK-1 antigen expressed in prostate cancer tissue. The anti-HNK-1 antibody is known to only recognize the epitope present in the carbohydrate moiety (not the peptide chain) of MUC18 and other cell surface proteins [Shih *et al.* (1994) *Cancer Res.* 54: 2514-2520]. It is well documented in the art that the HNK-1 antigen is expressed in many cell types and that its reactivity does not necessarily indicate that the epitope recognized is associated with MUC18 [Shih *et al.* (1994) *Cancer Research* 54:2514-2520; Ong *et al.* (2002) *JBC* 277:18182-90]. Accordingly, an ordinary person skilled in the art could not have been able to make the invention based on the teachings of Rubenstein *et al.*

Withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Claim Rejections under 35 U.S.C. §103:

Claims 2, 4, 7-10, 12 and 20 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Rubenstein *et al.* in view of Liu *et al.*, Shih *et al.*, US patents 5,807,978 and 6,057,105, and the annotation in the Swiss Protein Database. Applicant respectfully traverses this rejection.

Claims 4, 7-10, and 20 have been canceled without prejudice. Claims 2 and 12 have been amended and new claim 21 has been entered. Applicant submits that claims 2, 12, and 21 are not obvious over the cited references. None of the cited references teaches or suggests that a risk for metastasis of a prostate cancer cell can be predicted by measuring the level of expression of MUC18 polypeptide using antibodies specific for an epitope derived from the amino acid sequence given in SEQ ID NO: 2.

Liu *et al.* used the monoclonal antibodies against HNK-1 antigen, as did Rubenstein *et al.*, and found that the antibody reactivity was decreased or absent with the increasing pathological grades of prostate cancer. In contrast, the present application teaches that the level of the MUC18 polypeptide is increased as the prostate cancer cell metastasizes and thus the expression of MUC18 can be used as a predictor for a risk as to whether a given prostate cancer cell would likely become metastatic. Further, nothing in Rubenstein *et al.* suggests that the MUC18 expression alone can be used as a predictor for a risk for metastasis for a given prostate cancer cell. The findings of Liu *et al.* may be due to the use of the antibodies used, *i.e.*, antibodies recognizing the carbohydrate epitope as discussed above. Nonetheless, a person of ordinary skill in the art cannot find suggestion or motivation in Liu *et al.* to make and/or use the invention. Again, Shih *et al.* describes the Leu-7 (*i.e.*, HNK-1) as an epitope of the melanoma-associated antigen. There is no mention or suggestion of prostate cancer in the Shih *et al.* There is no teaching or suggestion that the level of the MUC18 polypeptide in a given prostate cancer cell can be used as a risk predictor for metastasis of the prostate cancer cell in either of the cited US patents.

Based on the foregoing, Applicant submits that claims 2, 12, and 21 are not *prima facie* obvious over the cited references. Withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Claim Rejections under 35 U.S.C. §112:

Claims 2, 4, 5, 7-12, and 20 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the Specification in such a way as to enable one skilled in the art to make and/or use the invention or to convey to a skilled artisan that the inventor had possession of the claimed invention when this application was filed. Applicant respectfully traverses this rejection.

With the entry of this Amendment, claims 2, 5, 12, and 21 remain in prosecution. Applicant submits that the pending claims define the invention such that the issues raised in the Office Action are no longer applicable. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 2, 4, 5, 7-12, and 20 are further rejected under 35 U.S.C. 112, second paragraph. Claims 2, 5, and 12 have been amended for improved clarity. Claims 4, 7-11, and 20 have been canceled without prejudice. New claim 21 is considered to be definite and clear. The terms that were alleged to be vague and indefinite in the Office Action are no longer recited in the pending claims. Withdrawal of the rejection under 35 U.S.C. 112, second paragraph, is respectfully requested.

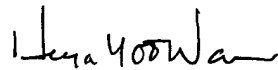
Conclusion:

Based on the foregoing amendments and arguments, claims 2, 5, 12, and 20 are deemed to be in condition for allowance and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time and a check in the amount of \$55 as required under 37 C.F.R. §1.17(a)(3) for a small entity. However, if the amount submitted is incorrect, please charge any deficiency or credit overpayment to Deposit Account No. 07-1969.

Respectfully submitted,



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Docket No. 95-97

Marked Changes

09/653,961

Amendment of 1/21/03

In the Claims

2. (Twice amended) The method of claim [20] 21, wherein said prostate cancer cell is from a biopsy tissue sample from a patient for whom a prediction of metastasis of prostate cancer is sought.
5. (Thrice amended) The method of claim [4] 21, wherein the MUC18 antigen is a middle portion of the MUC18 polypeptide and consists of the amino acid residues of 211-376 of the amino acid sequence as set forth in SEQ ID NO: 2.
12. (Once amended) The method of claim [1] 21, wherein said prostate cancer cell is a cell line cell.